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(54) Title: NOVEL IMIDAZOPYRAZINES AS CYCLIN DEPENDENT KINASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides a novel class of imidazo[1,2-a]pyrazine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

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NOVEL IMIDAZOPYRAZINES AS CYCLIN DEPENDENT KINASE INHIBITORSField of the Invention

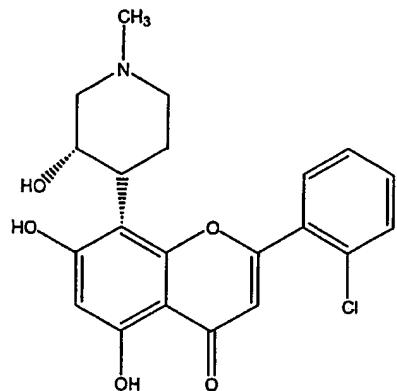
The present invention relates to imidazo[1,2-a]pyrazine compounds useful as protein kinase inhibitors (such as for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like), pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, and fungal diseases. This application claims the benefit 5 of priority from U.S. provisional patent application Serial No. 60/412,906, filed 10 September 23, 2002.

Background of the Invention

Protein kinase inhibitors include kinases such as, for example, the inhibitors 15 of the cyclin-dependent kinases (CDKs), mitogen activated protein kinase (MAPK/ERK), glycogen synthase kinase 3 (GSK3beta), and the like. The cyclin-dependent kinases are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Individual CDK's, such as, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK7, CDK8 and the like, perform distinct 20 roles in cell cycle progression and can be classified as either G1, S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer cells, and misregulation of CDK function occurs with high frequency in many important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently 25 misregulated in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. Checkpoints serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorigenesis. The CDK2 pathway influences tumorigenesis at the 30 level of tumor suppressor function (e.g. p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator,

cyclin E, and the inhibitor, p27, of CDK2 are either over – or underexpressed, respectively, in breast, colon, nonsmall cell lung, gastric, prostate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased CDK2 activity levels and poor overall
5 survival. This observation makes CDK2 and its regulatory pathways compelling targets for the development years, a number of adenosine 5'-triphosphate (ATP) competitive small organic molecules as well as peptides have been reported in the literature as CDK inhibitors for the potential treatment of cancers. U.S. 6,413,974, col. 1, line 23- col. 15, line 10 offers a good description of the various CDKs and
10 their relationship to various types of cancer.

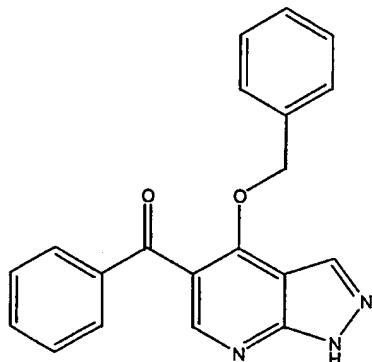
CDK inhibitors are known. For example, flavopiridol (Formula I) is a nonselective CDK inhibitor that is currently undergoing human clinical trials, A. M. Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.



15

Formula I

Other known inhibitors of the CDKs include, for example, olomoucine (J. Vesely *et al*, *Eur. J. Biochem.*, (1994) 224, 771-786) and roscovitine (I. Meijer *et al*, *Eur. J. Biochem.*, (1997) 243, 527-536). U.S. 6,107,305 describes certain pyrazolo[3,4-b] pyridine compounds as CDK inhibitors. An illustrative compound
20 from the '305 patent has the Formula II:



Formula II

K. S. Kim *et al*, *J. Med. Chem.* **45** (2002) 3905-3927 and WO 02/10162 disclose certain aminothiazole compounds as CDK inhibitors.

5 Pyrazolopyrimidines are known. For Example, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) **47** 928, *J. Med. Chem.*, (1977) **20**, 296, *J. Med. Chem.*, (1976) **19** 517 and *Chem. Pharm. Bull.*, (1962) **10** 620 disclose various pyrazolopyrimidines.

10 There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with CDKs. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

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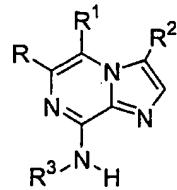
Summary of the Invention

In its many embodiments, the present invention provides a novel class of imidazo[1,2-a]pyrazine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound

25 having the general structure shown in Formula III:

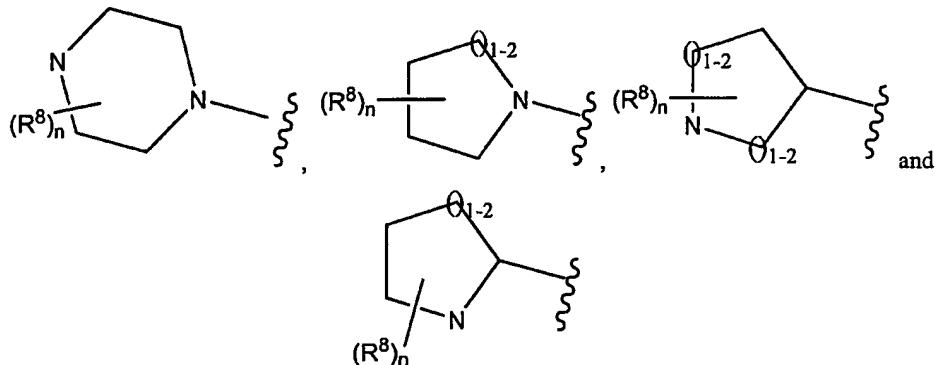
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Formula III

wherein:

R is selected from the group consisting of alkyl, CF₃, heteroaryl,
 5 heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, arylalkyl,
 -C(O)R⁷,

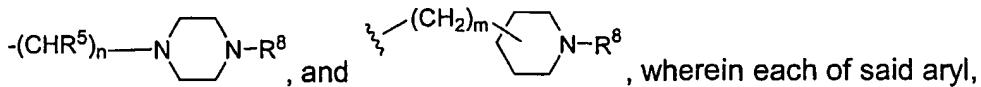


wherein each of said alkyl, heteroaryl, arylalkyl, cycloalkyl, heterocyclyl and the
 10 heterocyclyl moieties whose structures are shown immediately above for R can be
 unsubstituted or optionally independently substituted with one or more moieties
 which can be the same or different, each moiety being independently selected
 from the group consisting of halogen, alkyl, cycloalkyl, CF₃, CN, -OCF₃,
 -OR⁶, -C(O)R⁷, -NR⁵R⁶, -C(O₂)R⁶, -C(O)NR⁵R⁶, -(CHR⁵)_nOR⁶, -SR⁶, -S(O₂)R⁷,
 15 -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶;

R¹ is H, halogen or alkyl;R² is selected from the group consisting of H, halogen, CN, cycloalkyl,
 heterocyclyl, alkynyl and -CF₃;

R³ is selected from the group consisting of aryl (with the exception of
 20 phenyl), heteroaryl (with the exception of furyl), heterocyclyl, -(CHR⁵)_n-heteroaryl,
 -S(O₂)R⁶, -C(O)R⁶, -S(O₂)NR⁵R⁶, -C(O)OR⁶, -C(O)NR⁵R⁶,





heteroaryl and heterocycll can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl,

5 cycloalkyl, CF₃, CN, -OCF₃, -OR⁵, -NR⁵R⁶, -C(O₂)R⁵, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁶, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶, with the proviso that when R³ is $-(\text{CHR}^5)_n$ -heteroaryl, R² can additionally be alkyl;

R⁵ is H or alkyl;

R⁶ is selected from the group consisting of H, alkyl, aryl, heteroaryl,

10 arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl,

cycloalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁵R⁶, -CH₂OR⁵, -C(O₂)R⁵, -C(O)NR⁵R⁶,

15 -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶;

R⁷ is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more

20 moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁵R⁶, -CH₂OR⁵, -C(O₂)R⁵, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶;

R⁸ is selected from the group consisting of R⁶, -C(O)NR⁵R⁶,

25 -S(O₂)NR⁵R⁶, -C(O)R⁷, -C(O₂)R⁶, -S(O₂)R⁷ and -(CH₂)-aryl;

m is 0 to 4; and

n is 1-4.

The compounds of Formula III can be useful as protein kinase inhibitors and can be useful in the treatment and prevention of proliferative diseases, for

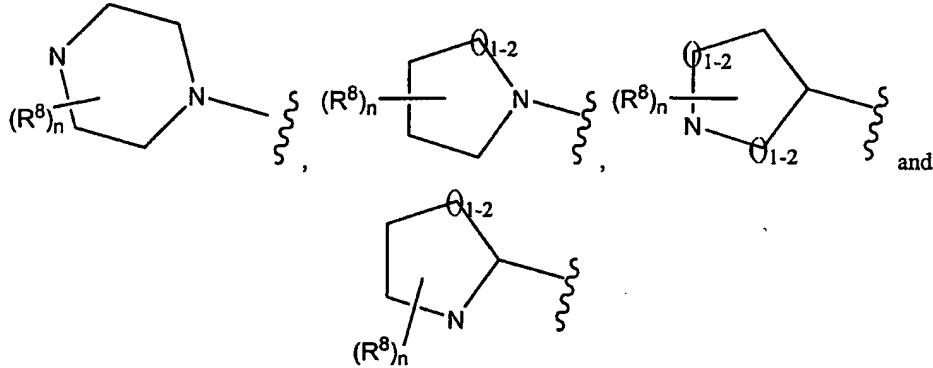
30 example, cancer, inflammation and arthritis. They may also be useful in the

treatment of neurodegenerative diseases such Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

Detailed Description

5 In one embodiment, the present invention discloses imidazo[1,2-a]pyrazine compounds which are represented by structural Formula III, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

10 In a preferred embodiment, R is selected from the group consisting of alkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, arylalkyl,

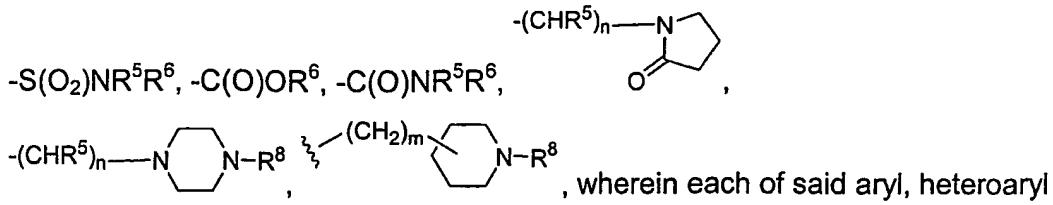


15 wherein each of said alkyl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl and the heterocyclyl moieties shown above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF₃, CN, -OCF₃, -OR⁶, -C(O)R⁷, -NR⁵R⁶, -C(O₂)R⁶, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶.

20 In another preferred embodiment, R¹ is H or halogen.

In another preferred embodiment, R² is selected from the group consisting of H, halogen, cycloalkyl, CN, alkynyl and -CF₃.

In another preferred embodiment, R³ is selected from the group consisting of aryl, heteroaryl, heterocyclyl, -(CHR⁵)_n-heteroaryl, -S(O₂)R⁶, -C(O)R⁶,



5 selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3 , CN ,
 $-\text{OCF}_3$, $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{S}(\text{O}_2)\text{R}^6$, and $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^7$.

In another preferred embodiment, R^5 is H or lower alkyl.

In another preferred embodiment, m is 0 to 2.

In another preferred embodiment, n is 1 to 3.

10 In an additional preferred embodiment, R is selected from the group
 consisting of methyl, ethyl, t-butyl, cyclohexylmethyl, benzyl and phenethyl.

In an additional preferred embodiment, R^1 is H, Br or methyl.

In an additional preferred embodiment, R^2 is F, Cl, Br, I, cyclohexyl or CF_3 .

In an additional preferred embodiment, R^3 is (pyrid-2-yl)methyl, (pyrid-3-

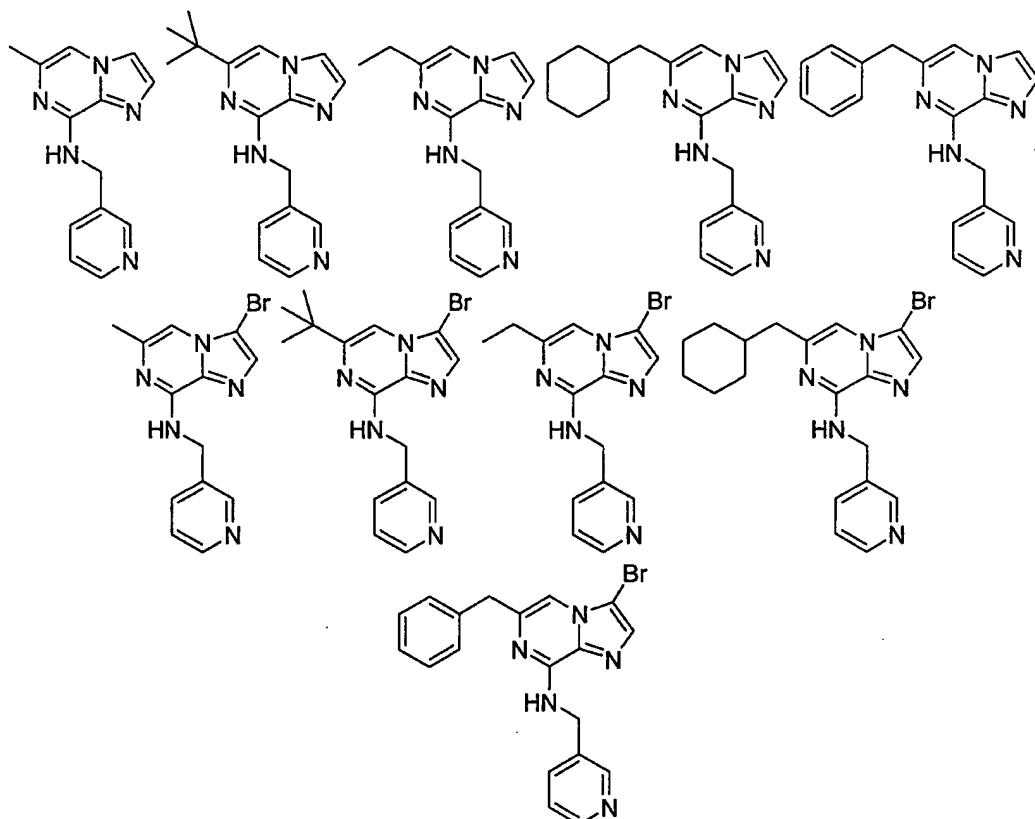
15 (yl)methyl, (pyrid-4-yl)methyl, thien-2-yl or thien-3-yl, wherein said pyridyl or thiényl
 can be unsubstituted or optionally substituted with one or more moieties which can
 be the same or different, each moiety being independently selected from the group
 consisting of F, Cl, Br, CF_3 , lower alkyl, methoxy and CN.

In an additional preferred embodiment, R^5 is H.

20 In an additional preferred embodiment, m is 0.

In an additional preferred embodiment, n is 1 or 2.

A particularly preferred group of compounds are shown in **Table 1**.

Table 1

5

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

- "Patient" includes both human and animals.
- "Mammal" means humans and other mammalian animals.
- 10 "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain.
- Branched means that one or more lower alkyl groups such as methyl, ethyl or 15 propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl,

cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain.

5 "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently

10 15 selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thieryl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl,

thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl,
5 pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.
10

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is toyl. The bond to the parent moiety is through the aryl.
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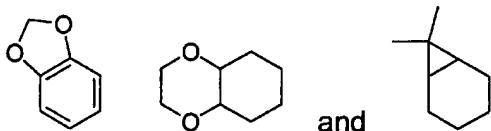
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms.
20 The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as
25 well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine.
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on
30 the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl,

heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-

5 NH₂, -C(=NH)-NH₂, -C(=NH)-NH(alkyl), Y₁Y₂N-, Y₁Y₂N-alkyl-, Y₁Y₂NC(O)-, Y₁Y₂NSO₂- and -SO₂NY₁Y₂, wherein Y₁ and Y₂ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -C(CH₃)₂- and the like which form moieties such as, for example:

10 10



"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic

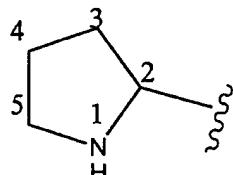
15 15 ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocycls contain about 5 to about 6 ring atoms. The prefix

20 20 aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring

25 25 system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl,

30 30 tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



5

there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



10 are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

15 "Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

20 "Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

25 "Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

15 "Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

20 "Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

25 "Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxy carbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

30 "Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O₂)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O₂)- group. The bond to the parent moiety is 5 through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of 10 substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the 15 specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained 20 from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen 25 atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by 30 reference to standard textbooks such as, for example, T. W. Greene *et al.*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R², etc.) occurs more than one time in any constituent or in Formula III, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula III or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula III can form salts which are also within the scope of this invention. Reference to a compound of Formula III herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic

and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and
5 are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula III may be formed, for example, by reacting a compound of Formula III respectively with an amount of acid or base, such as an equivalent amount, in a medium such as one in which
10 the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, 15 phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences*
20 (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

25 Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be
30 quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides,

bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are
5 considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula III, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

10 All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence
15 of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other
20 selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

25 The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula III can be inhibitors of protein kinases such as, for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like. The cyclin dependent kinases (CDKs) include, for
30 example, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 and CDK8. The novel compounds of Formula III are expected to be useful in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases,

fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974 cited earlier, the disclosure of which is incorporated herein.

5 More specifically, the compounds of Formula III can be useful in the treatment of a variety of cancers, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

10 hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

15 hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

20 tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of CDKs in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in
25 the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation
30 rejection, endotoxic shock, and fungal infections.

Compounds of Formula III may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that CDK5 is involved in the phosphorylation of tau protein (*J. Biochem.*, (1995) 117, 741-749).

Compounds of Formula III may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of Formula III, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpevirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formula III, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formula III may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formula III may also be useful in inhibiting tumor angiogenesis and metastasis.

Compounds of Formula III may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf 1, MEK1, MAP kinase, EGF receptor, 5 PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

Another aspect of this invention is a method of treating a mammal (e.g., human) having a disease or condition associated with the CDKs by administering a therapeutically effective amount of at least one compound of Formula III, or a 10 pharmaceutically acceptable salt or solvate of said compound to the mammal.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula III. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound.

15 The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more of anti-cancer treatments such as radiation therapy, and/or one or more anti-cancer agents selected from the group consisting of cytostatic agents, cytotoxic agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin));
20 taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11), camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methotrexate); alkylating
25 agents (such as temozolamide (TEMODAR™ from Schering-Plough Corporation, Kenilworth, New Jersey), cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASAR™(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, or SCH 66336 from Schering-Plough Corporation,
30 Kenilworth, New Jersey), tipifarnib (Zarnestra® or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (a farnesyl protein

transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); signal transduction inhibitors (such as, Iressa (from Astra Zeneca Pharmaceuticals, England), Tarceva (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC™ (C-abl kinase inhibitor from Novartis

5 Pharmaceuticals, East Hanover, New Jersey); interferons such as, for example, intron (from Schering-Plough Corporation), Peg-Intron (from Schering-Plough Corporation); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, cytoxan, and gemcitabine.

Other anti-cancer (also known as anti-neoplastic) agents include but are
10 not limited to Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaceuticals, France),
15 Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone,
20 Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or
25 Hexamethylmelamine.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. For example, the CDC2 inhibitor olomoucine has been found to act synergistically with
30 known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897). Compounds of Formula III may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate.

The invention is not limited in the sequence of administration; compounds of Formula III may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of
5 administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate thereof, and an amount of one or more anti-cancer treatments and anti-cancer agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.
10

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified
15 pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable
20 carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised
25 of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A.
30 Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions 5 for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, 10 shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or 15 reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously. Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing 20 appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the 25 particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and 30 administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated

according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

5 Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

10 Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one anticancer therapy and/or anti-cancer agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

15 The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a
20 Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me₄Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum
25 C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH₃CN, 5 min – 95% CH₃CN, 7 min – 95% CH₃CN, 7.5 min – 10% CH₃CN, 9 min – stop. The retention time and observed parent ion are given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

30 Thin layer chromatography: TLC
dichloromethane: CH₂Cl₂
ethyl acetate: AcOEt or EtOAc

methanol: MeOH

trifluoroacetate: TFA

triethylamine: Et₃N or TEA

butoxycarbonyl: n-Boc or Boc

5 nuclear magnetic resonance spectroscopy: NMR

liquid chromatography mass spectrometry: LCMS

high resolution mass spectrometry: HRMS

milliliters: mL

millimoles: mmol

10 microliters: μ L

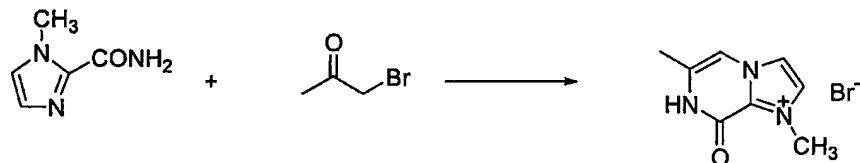
grams: g

milligrams: mg

room temperature or rt (ambient): about 25°C.

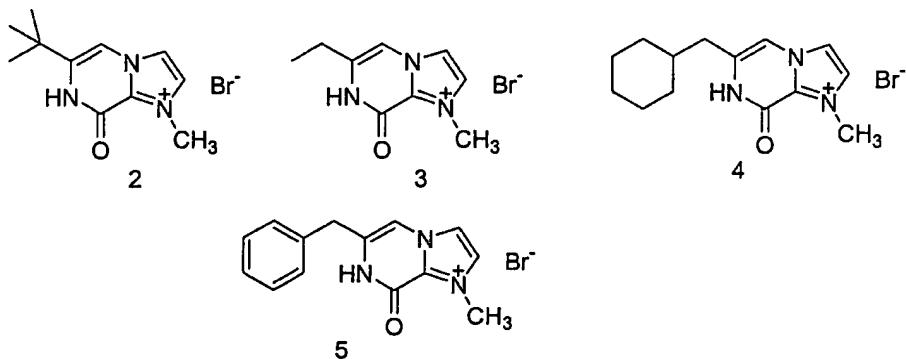
15 **EXAMPLES**

PREPARATIVE EXAMPLE 1



A mixture of 1-methylimidazole-2-carboxamide (1 equiv.) and
bromoacetone (1.2 eq) in anhydrous CH₃CN is stirred and refluxed under N₂ for 1
20 day. The solvent is evaporated and the pure product is obtained after column
chromatography on silica gel with CH₂Cl₂:7 N NH₃ in MeOH.

PREPARATIVE EXAMPLES 2-5:



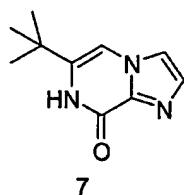
These compounds are prepared by essentially same procedure set forth in Preparative Example 1.

PREPARATIVE EXAMPLE 6:

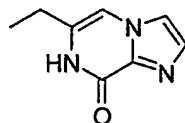


5 A mixture of the product from Preparative Example 1 (1 eq.) and imidazole (25 eq.) is stirred under N₂ at 175°C for 20 hr. The imidazole is distilled off in a vacuum and the residue is purified by column chromatography on silica gel with CH₂Cl₂:7 N NH₃ in MeOH. Pure product is obtained.

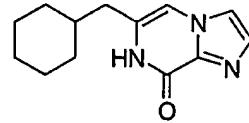
PREPARATIVE EXAMPLES 7-10:



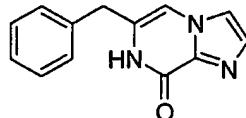
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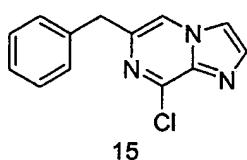
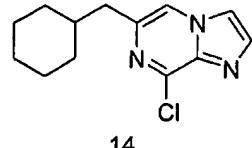
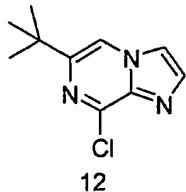
These compounds are prepared by essentially same procedure set forth in Preparative Example 6.

PREPARATIVE EXAMPLE 11:

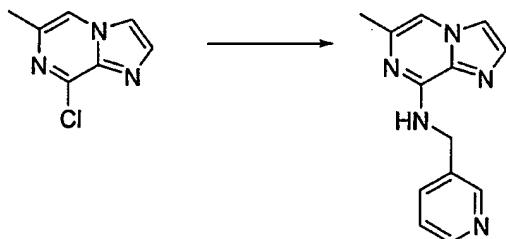


15 A mixture of the product from Preparative Example 6 (1 eq.) and pyridine (0.75 eq) in POCl₃ (30 eq.) is stirred and refluxed under N₂ for 5 hrs. The mixture is poured into ice, neutralized with 10% aqueous solution of NaOH, and extracted with CH₂Cl₂. The extracts are dried over Na₂SO₄, filtered and the solvent is evaporated. Column chromatography on silica gel with CH₂Cl₂/EtOAc gives pure product.

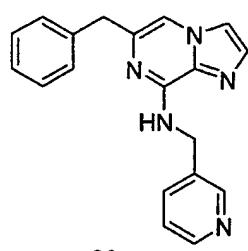
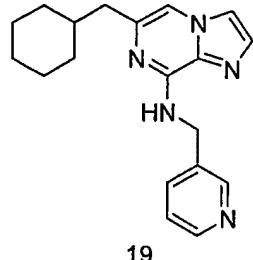
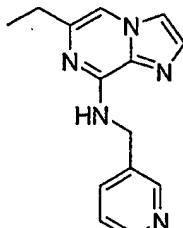
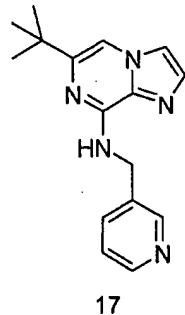
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PREPARATIVE EXAMPLES 12-15:

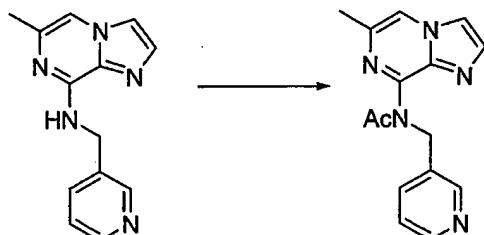
These compounds are prepared by essentially same procedure set forth in Preparative Example 11.

5 EXAMPLE 16:

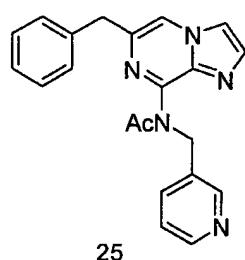
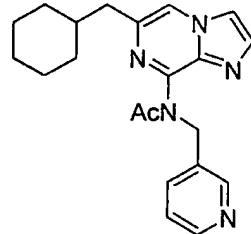
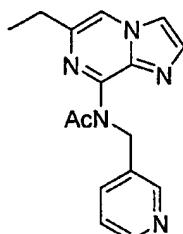
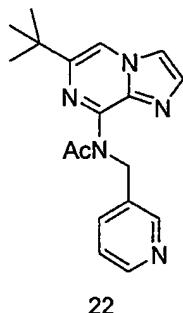
A mixture of the product from Preparative Example 11 (1 eq.), 3-(aminomethyl)pyridine (1.1 eq), diisopropylethylamine (20 eq), and anhydrous dioxane is stirred at 90°C under N₂ for 48 hr. The solvent is evaporated and the
 10 residue is purified by column chromatography on silica gel with CH₂Cl₂/MeOH/conc. aqueous NH₄OH. Pure product is obtained.

EXAMPLES 17-20:

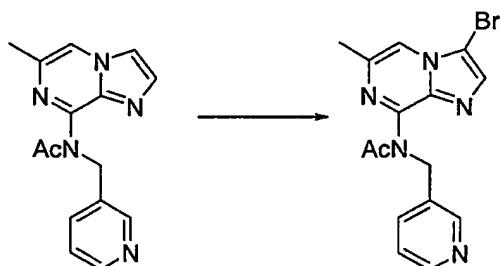
These compounds are prepared by essentially same procedure set forth in Preparative Example 16.

5 EXAMPLE 21:

A mixture of the product from Preparative Example (1 eq.), acetyl chloride (3 eq), diisopropylethylamine (6 eq), and anhydrous 1,2-dichloroethane is refluxed under N₂ for 24 hr. The mixture is poured into saturated aqueous NaHCO₃, extracted with CH₂Cl₂ and the extracts are dried over Na₂SO₄. The solvent is evaporated and the residue is purified by column chromatography on silica gel with CH₂Cl₂/EtOAc to yield pure product.

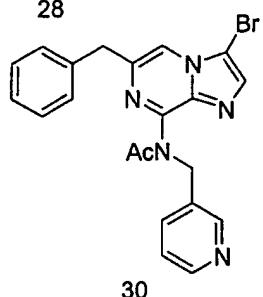
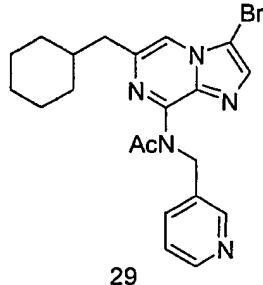
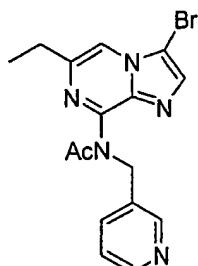
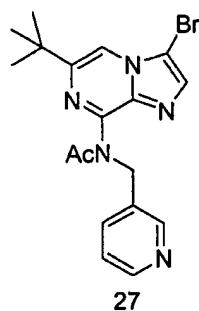
EXAMPLES 22-25:

These compounds are prepared by essentially same procedure set forth in Preparative Example 21.

5 EXAMPLE 26:

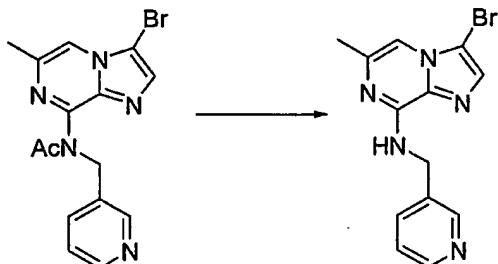
A solution of NBS (1 eq.) in anhydrous CH₃CN is added under N₂ to a stirred solution of the product from Preparative Example (1 eq.) in anhydrous CH₃CN. The mixture is stirred at 25°C for 2 hr and the solvent is then evaporated.

10 Chromatography on silica gel with EtOAc/MeOH affords the product.

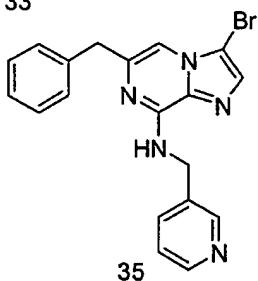
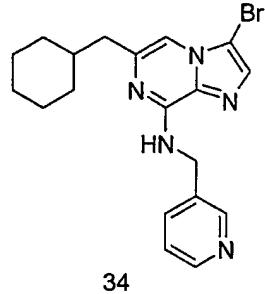
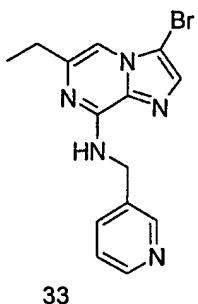
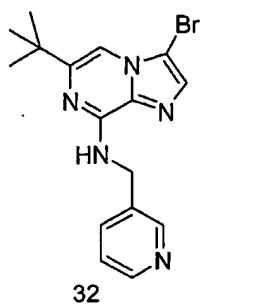
EXAMPLES 27-30:

These compounds are prepared by essentially same procedure set forth in

Example 26.

5 EXAMPLE 31:

A mixture of the product from Preparative Example (1 eq.), and potassium carbonate (10 eq.) in MeOH, 1,2-dimethoxyethane, and H₂O is stirred at 50°C under N₂ for 2 hr. CH₂Cl₂ is then added, the mixture is dried over Na₂SO₄, and 10 filtered. The solvent is evaporated and the residue is purified by column chromatography on silica gel with EtOAc/MeOH to yield pure product.

EXAMPLES 32-35:

These compounds are prepared by essentially same procedure set forth in Preparative Example 31.

5 **ASSAY:** The assay on the compounds of the invention can be performed as described below:

BACULOVIRUS CONSTRUCTIONS: Cyclins A and E are cloned into pVL1393 (Pharmingen, La Jolla, California) by PCR, with the addition of 5 histidine residues at the amino-terminal end to allow purification on nickel resin.

10 The expressed protein is approximately 46kDa (cyclin E) and 50kDa (cyclin A) in size. CDK2 was cloned into pVL1393 by PCR, with the addition of a haemagglutinin epitope tag at the carboxy-terminal end (YDVPDYAS). The expressed protein is approximately 34kDa in size.

ENZYME PRODUCTION: Recombinant baculoviruses expressing cyclins

15 A, E and CDK2 are co-infected into SF9 cells at an equal multiplicity of infection (MOI=5), for 48 hrs. Cells are harvested by centrifugation at 1000 RPM for 10 minutes, then pellets lysed on ice for 30 minutes in five times the pellet volume of lysis buffer containing 50mM Tris pH 8.0, 150mM NaCl, 1% NP40, 1mM DTT and protease inhibitors (Roche Diagnostics GmbH, Mannheim, Germany).

20 Lysates are spun down at 15000 RPM for 10 minutes and the supernatant retained. 5ml of nickel beads (for one liter of SF9 cells) are washed three times in

lysis buffer (Qiagen GmbH, Germany). Imidazole is added to the baculovirus supernatant to a final concentration of 20mM, then incubated with the nickel beads for 45 minutes at 4° C. Proteins are eluted with lysis buffer containing 250mM imidazole. Eluate is dialyzed overnight in 2 liters of kinase buffer
5 containing 50mM Tris pH 8.0, 1mM DTT, 10mM MgCl₂, 100uM sodium orthovanadate and 20% glycerol. Enzyme is stored in aliquots at -70°C.

IN VITRO KINASE ASSAY: CDK2 kinase assays (either cyclin A or E-dependent) are performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme is diluted to a final concentration of 50 µg/ml in
10 kinase buffer containing 50mM Tris pH 8.0, 10mM MgCl₂, 1mM DTT, and 0.1mM sodium orthovanadate. The substrate used in these reactions is a biotinylated peptide derived from Histone H1 (from Amersham, UK). The substrate is thawed on ice and diluted to 2 µM in kinase buffer. Compounds are diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 µl of the 50 µg/ml
15 enzyme solution (1 µg of enzyme) and 20 µl of the 2 µM substrate solution are mixed, then combined with 10 µl of diluted compound in each well for testing. The kinase reaction is started by addition of 50 µl of 2 µM ATP and 0.1 µCi of 33P-ATP (from Amersham, UK). The reaction is allowed to run for 1 hour at room temperature. The reaction is stopped by adding 200 µl of stop buffer containing
20 0.1% Triton X-100, 1mM ATP, 5mM EDTA, and 5 mg/ml streptavidine coated SPA beads (from Amersham, UK) for 15 minutes. The SPA beads are then captured onto a 96-well GF/B filter plate (Packard/Perkin Elmer Life Sciences) using a Filtermate universal harvester (Packard/Perkin Elmer Life Sciences.). Non-specific signals are eliminated by washing the beads twice with 2M NaCl
25 then twice with 2 M NaCl with 1% phosphoric acid. The radioactive signal is then measured using a TopCount 96 well liquid scintillation counter (from Packard/Perkin Elmer Life Sciences).

IC₅₀ DETERMINATION: Dose-response curves are plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of
30 inhibitory compounds. Concentration of compound is plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated

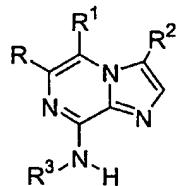
samples. To generate IC₅₀ values (by using cyclin A or cyclin E using the above-described assay), the dose-response curves are then fitted to a standard sigmoidal curve and IC₅₀ values are derived by nonlinear regression analysis.

While the present invention has been described with in conjunction with the 5 specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS

What is claimed is:

1. A compound represented by the structural formula



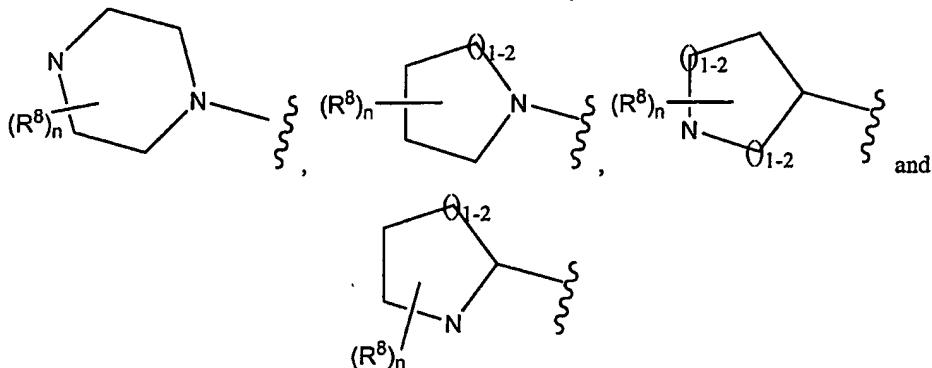
5

Formula III

wherein:

R is selected from the group consisting of alkyl, CF₃, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, arylalkyl, -C(O)R⁷,

10



wherein each of said alkyl, heteroaryl, arylalkyl, cycloalkyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties

15

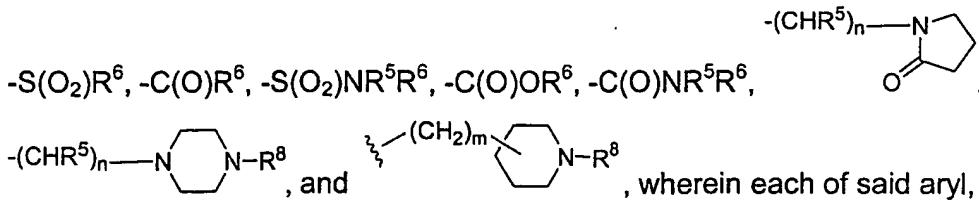
which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF₃, CN, -OCF₃, -OR⁶, -C(O)R⁷, -NR⁵R⁶, -C(O₂)R⁶, -C(O)NR⁵R⁶, -(CHR⁵)_nOR⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶;

R¹ is H, halogen or alkyl;

20

R² is selected from the group consisting of H, halogen, CN, cycloalkyl, heterocyclyl, alkynyl and -CF₃;

R³ is selected from the group consisting of aryl (with the exception of phenyl), heteroaryl (with the exception of furyl), heterocyclyl, -(CHR⁵)_n-heteroaryl,



heteroaryl and heterocyclyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being

5 independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF₃, CN, -OCF₃, -OR⁵, -NR⁵R⁶, -C(O₂)R⁵, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁶, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶, with the proviso that when R³ is -(CHR⁵)_n-heteroaryl, R² can additionally be alkyl;

R⁵ is H or alkyl;

10 R⁶ is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl,

15 cycloalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁵R⁶, -CH₂OR⁵, -C(O₂)R⁵, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶:

R⁷ is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl

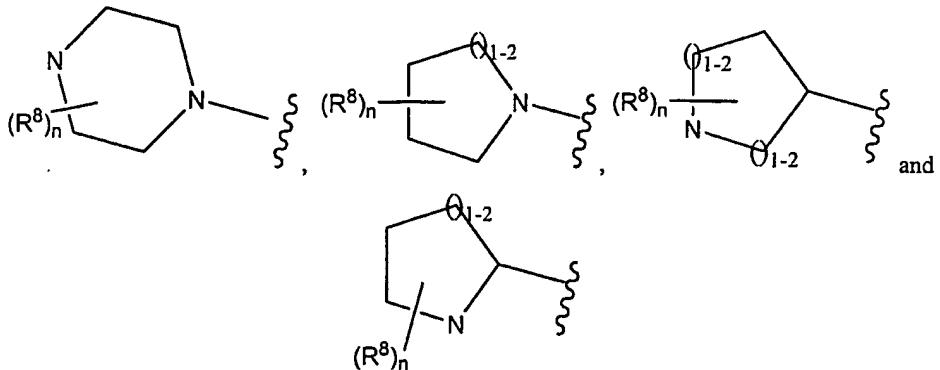
20 and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁵R⁶, -CH₂OR⁵, -C(O₂)R⁵, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶;

25 R⁸ is selected from the group consisting of R⁶, -C(O)NR⁵R⁶, -S(O₂)NR⁵R⁶, -C(O)R⁷, -C(O₂)R⁶, -S(O₂)R⁷ and -(CH₂)-aryl;

m is 0 to 4; and

n is 1-4.

2. R is selected from the group consisting of alkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, arylalkyl,



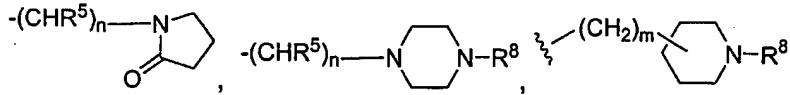
wherein each of said alkyl, heteroaryl, cycloalkyl, arylalkyl, heterocycll and the heterocycll moieties shown above for R can be unsubstituted or optionally

5 independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF₃, CN, -OCF₃, -OR⁶, -C(O)R⁷, -NR⁵R⁶, -C(O₂)R⁶, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶.

10 R¹ is H or halogen;

R² is selected from the group consisting of H, halogen, cycloalkyl, CN, alkynyl and -CF₃;

R³ is selected from the group consisting of aryl, heteroaryl, heterocycll, -(CHR⁵)_n-heteroaryl, -S(O₂)R⁶, -C(O)R⁶, -S(O₂)NR⁵R⁶, -C(O)OR⁶, -C(O)NR⁵R⁶,



15 , wherein each of

said aryl, heteroaryl and heterocycll can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF₃, CN, -OCF₃, -N(R⁵)C(O)R⁷, -C(O)NR⁵R⁶, -S(O₂)R⁶, and -N(R⁵)C(O)R⁷;

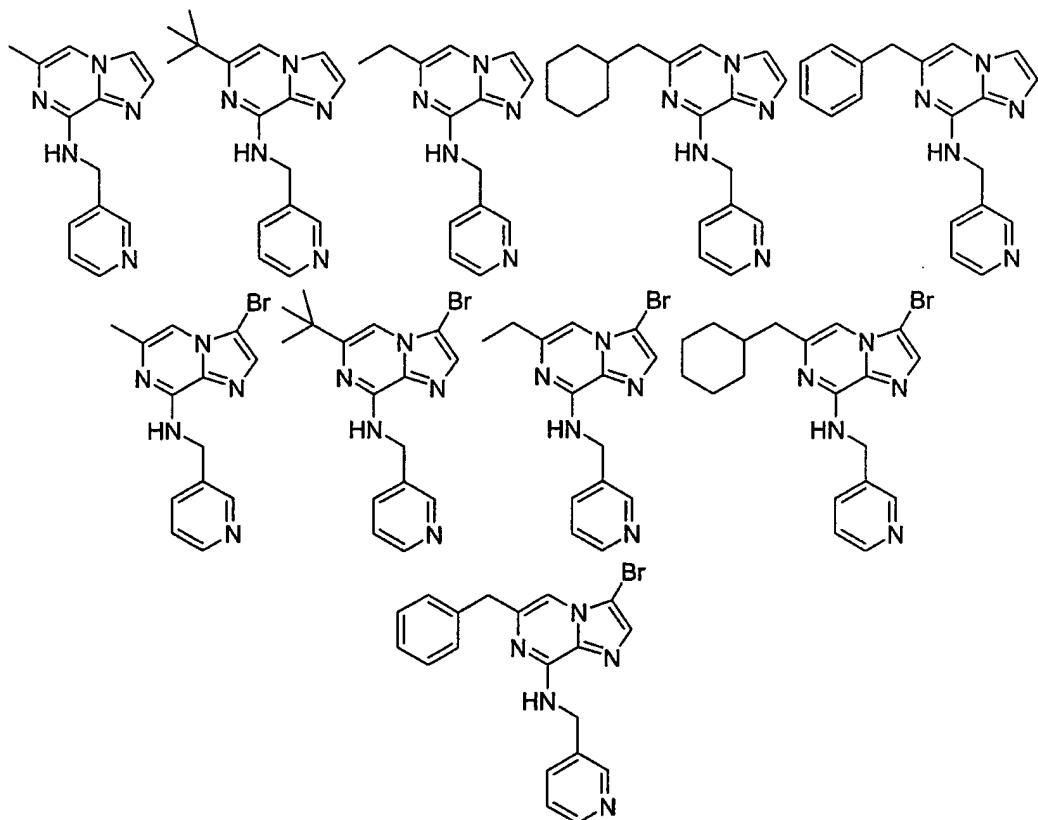
20 R⁵ is H or lower alkyl;

m is 0 to 2; and

n is 1 to 3.

3. The compound of claim 2, wherein R is alkyl, arylalkyl or cycloalkylalkyl.

4. The compound of claim 3, wherein R is selected from the group consisting of methyl, ethyl, t-butyl, cyclohexylmethyl, benzyl and phenethyl.
5. The compound of claim 2, wherein R¹ is H.
6. The compound of claim 2, wherein R¹ is methyl.
- 5 7. The compound of claim 2, wherein R² is H, F, Cl, Br or I.
8. The compound of claim 7, wherein R² is Br.
9. The compound of claim 8, wherein R³ is (pyrid-2-yl)methyl, (pyrid-3-yl)methyl, (pyrid-4-yl)methyl, thien-2-yl or thien-3-yl, wherein said pyridyl and thienyl can be unsubstituted or optionally independently substituted with one or more
- 10 moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Cl, Br, CF₃, lower alkyl, methoxy and CN.
10. The compound of claim 9, wherein R³ is (pyrid-2-yl)methyl.
11. The compound of claim 9, wherein R³ is (pyrid-3-yl)methyl.
12. The compound of claim 9, wherein R³ is (pyrid-4-yl)methyl.
- 15 13. The compound of claim 2, wherein m is 0.
14. The compound of claim 2, wherein n is 1.
15. A compound of the formula:



- 5 or a pharmaceutically acceptable salt or solvate thereof.
- 16. A method of inhibiting one or more cyclin dependent kinases, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such inhibition.
- 17. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such treatment.
- 18. The method of claim 17, wherein said cyclin dependent kinase is CDK2.
- 19. The method of claim 17, wherein said cyclin dependent kinase is mitogen activated protein kinase (MAPK/ERK).
- 20. The method of claim 17, wherein said cyclin dependent kinase is glycogen synthase kinase 3 (GSK3beta).
- 21. The method of claim 17, wherein said disease is selected from the group consisting of:

cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia;

fibrosarcoma, rhabdomyosarcoma;

astrocytoma, neuroblastoma, glioma and schwannomas; melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoanthoma, thyroid follicular cancer and Kaposi's sarcoma.

22. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering to a mammal in need of such treatment

an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof;

and

an amount of at least one second compound, said second compound being an anti-cancer agent;

wherein the amounts of the first compound and said second compound result in a therapeutic effect.

23. The method of claim 22, further comprising radiation therapy.

24. The method of claim 22, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, 5FU, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine,

6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycodormycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol,

5 Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin,

10 Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

25. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 in combination with at least one pharmaceutically acceptable carrier.

15 26. The pharmaceutical composition of claim 25, additionally comprising one or more anti-cancer agents selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil,

20 methotrexate, 5FU, temozolamide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin,

25 Dacarbazine, Flouxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycodormycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone,

30 Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine,

Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

5 27. A compound of claim 1 in purified form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/29456

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/5025 A61K31/407 A61K31/4406 A61K31/4427 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 2002 060492 A (CYTOPIA PTY LTD) 8 August 2002 (2002-08-08)</p> <p>* claims 24-34; see especially compounds 2, 6, 7 & 9 on page 83 *</p> <p>* pages 53 & 54, compounds 34, 39, 40 and 42 *</p> <p>-----</p>	1-5, 7, 9, 16-27

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2004	05/02/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Elliott, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/29456

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 16-24 are directed to methods of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US 03/29456

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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